

# Etanercept Ameliorates Sarcoidosis Arthritis and Skin Disease

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**ABSTRACT.** Sarcoidosis is a systemic disorder of unknown etiology characterized by its pathological hallmark, the noncaseating granuloma. In granulomatous diseases, the proinflammatory peptide mediators, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), are increased in the blood and fluids surrounding the activated macrophages. We describe a patient with chronic sarcoidosis arthropathy and lupus pernio resistant to corticosteroids and disease modifying antirheumatic agents, who responded to the addition of etanercept. We discuss the possible mechanisms of action of anti-TNF agents in granulomatous diseases and suggest that chronic, resistant sarcoidosis requires combination immunosuppressive therapy. (J Rheumatol 2003;30:1864–7)

*Key Indexing Terms:*  
SARCOIDOSIS

ETANERCEPT

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, which exhibits noncaseating granulomas in the lungs, skin, bone, and other tissues<sup>1</sup>. Production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by alveolar macrophages is increased in sarcoidosis, which with elevated serum concentrations of the soluble interleukin 2 receptors predicts progression of disease in this disorder<sup>2–4</sup>. We describe a case of resistant cutaneous and bone sarcoidosis that markedly improved on treatment with etanercept, a recombinant fusion protein of two p75 soluble TNF- $\alpha$  receptors and the Fc portion of human IgG.

## CASE REPORT

A 50-year-old African-American woman presented to our medical center with pain and swelling of her joints and a disfiguring facial rash. Ten years previously, she had developed a persistent, nonproductive cough and nodular lesions on her face. The chest radiograph showed bilateral hilar adenopathy. Biopsy of the skin showed noncaseating granulomas with negative cultures for fungus and acid-fast bacillus. A diagnosis of sarcoidosis was made, which prompted treatment with prednisone and local intralesional steroid injections. Five years later, she developed pain and swelling of her hands and feet. "Sausage" digits were noted, which responded minimally to nonsteroidal antiinflammatory agents (NSAID)

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and oral prednisone. Over the next 5 years, she continued to have morning stiffness and joint swelling despite high dose prednisone up to 60 mg daily and hydroxychloroquine 200 mg twice a day.

She denied any chronic back pain, bloody diarrhea, or recent urinary tract infections. Examination revealed normal vital signs. The skin displayed irregular hyper and hypo-pigmented lesions over the face (Figure 1A), arms, back, and thighs. Musculoskeletal examination revealed dactylitis of her hands and feet, with asymmetrical synovitis involving the distal and proximal interphalangeal joints. The chest was clear and there was no lymphadenopathy or splenomegaly. She had normal renal and hepatic function; other laboratory and serological data are summarized in Table 1. Chest radiograph did not reveal hilar adenopathy or interstitial infiltrates. Radiographs of the hand and foot showed minimal soft tissue swelling, with trabecular changes and cystic changes in the middle and distal phalanges (Figure 2). A diagnosis of sarcoidosis presenting as lupus pernio and arthropathy was made after review of the skin biopsy from January 1992.

Therapy was started with rofecoxib 25 mg daily and oral methotrexate (MTX) in increasing doses, up to 17.5 mg once weekly over next 3 months. Despite mild improvement in her morning stiffness and dactylitis, she developed gastrointestinal symptoms and oral ulcers, which persisted even after increasing the daily dose of folic acid. Accordingly, etanercept (Enbrel<sup>®</sup>) at a dose of 25 mg twice weekly was added to prednisone 30 mg once daily, hydroxychloroquine 200 mg twice daily, and MTX 15 mg once weekly. Within 2 months of starting this regimen, she noted marked improvement. The prednisone was rapidly tapered and within 3 months it was discontinued along with hydroxychloroquine. MTX was decreased to 5 mg/week. Morning stiffness decreased from 45 min to about 10 min. The skin lesions became nontender, less swollen, and markedly smaller (Figure 1B). The decrease in tenderness and swelling in her hands and feet allowed her to return to work. Six months later, she developed cellulitis of the right lower extremity. Etanercept was discontinued transiently while broad spectrum antibiotics were administered. Repeat hand radiographs showed stabilization of the bone disease (not shown). She has continued with etanercept 25 mg twice weekly, MTX 5 mg once weekly, and rofecoxib 25 mg daily, for about 18 months. During her last clinic visit, she had no evidence of disease activity.

## DISCUSSION

Sarcoidosis is a systemic disorder of unknown cause that is characterized by its pathological hallmark, the noncaseating



Figure 1. Lesions on the patient's face before therapy with etanercept (A) and after therapy with etanercept (B).

Table 1. Laboratory and serological findings.

Test	Value	Reference
WBC, $\times 10^3/\mu\text{l}$	5.77	4–11
Hematocrit, %	29	34–42
Platelets $\times 10^3/\mu\text{l}$	221	148–340
ESR, mm/h	53	0–20
Serum calcium, mg/dl	8.8	8.5–10
CPK, U/l	116	40–180
Serum ACE, U/l	140	< 100
Urinalysis	Neg	Neg
Antinuclear antibody	1:80	< 1:40
Anti-double stranded DNA	Neg	Neg
Anti-Smith/ribonucleoprotein	Neg	Neg
Rheumatoid factor	Neg	Neg

ACE: angiotensin converting enzyme.

granuloma<sup>1</sup>. Respiratory tract involvement occurs at some time in the course of nearly all cases of sarcoidosis. Cutaneous disease usually presents either acutely with erythema nodosum, or chronically with lupus pernio, nodular lesions, or plaque lesions<sup>5</sup>. Lupus pernio is associated with extracutaneous involvement, particularly sarcoid dacrylitis<sup>5</sup>.

Rheumatic manifestations of sarcoidosis include arthropathy, bone disease, myopathy, and vasculitis<sup>6,7</sup>. Acute polyarthrits is the most common form of joint involvement. It may be associated with bilateral hilar lymph node enlargement and erythema nodosum (Lofgren's syndrome) or occur in isolation<sup>8</sup>. Chronic polyarthrits can present in different ways, including nondeforming arthritis and Jaccoud's arthropathy<sup>9</sup>. The presence of chronic arthritis is frequently associated with elevated angiotensin-converting enzyme (ACE), as in our patient<sup>10</sup>.

Bone disease affects roughly 5% of patients with sarcoidosis<sup>11</sup>. The chronic bone lesions are usually cystic or sclerotic in the proximal and distal phalanges. Radiographs show lytic bone lesions within the metaphyses of the phalanges, with remodeling of the cortex and occasionally multiple fractures. Granulomatous skin lesions are present in a majority of patients with bone changes<sup>11</sup>.

Acute sarcoid arthropathy usually responds to NSAID<sup>9</sup>. The chronic form responds inconsistently to corticosteroids and disease modifying antirheumatic agents such as MTX, hydroxychloroquine, or cyclosporin A<sup>9,12</sup>.

Inhibitors of TNF- $\alpha$  are appealing treatment options for resistant sarcoidosis because TNF- $\alpha$  plays a pivotal role in

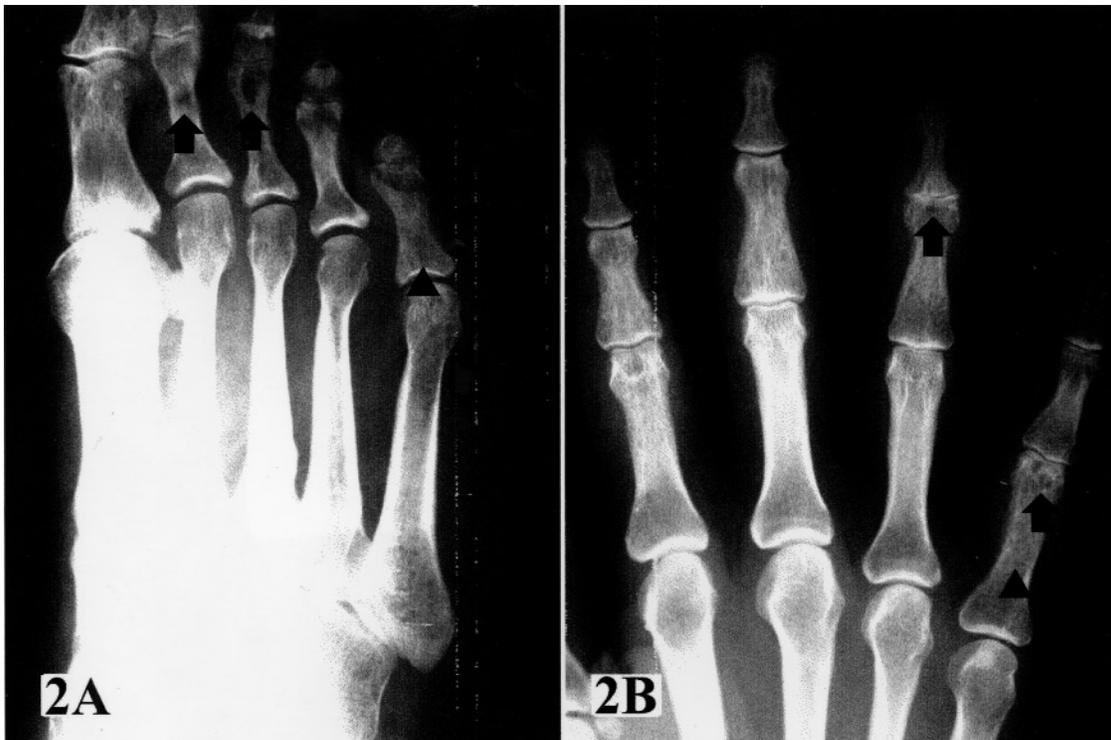


Figure 2. Radiographs of the patient's foot (A) and hand (B) show cystic (arrows) and trabecular (arrowheads) changes in the middle phalanges of the foot and the middle and proximal phalanges of the hand. Similar changes can be seen in other middle and distal phalanges of the foot (not marked).

granuloma formation<sup>13</sup>. The inflammatory process in sarcoidosis is accelerated by the release of TNF- $\alpha$  from alveolar macrophages<sup>2,14,15</sup>, which subsequently recruit and activate other monocytes, macrophages, and inflammatory cells and induce cell differentiation and apoptosis<sup>3,4</sup>. A recent case report described the favorable response to infliximab (monoclonal human-murine chimeric anti-TNF- $\alpha$  antibody) in a patient with resistant sarcoidosis who presented with protein-losing enteropathy and myopathy<sup>16</sup>. In addition, 2 cases of lupus pernio resistant to corticosteroids but responsive to infliximab have been reported<sup>17</sup>. Our patient's excellent response to etanercept supports the hypothesis that TNF- $\alpha$  may be one of the primary cytokines mediating the pathogenesis of sarcoidosis. Increases of both TNF- $\alpha$  expression and concentration have also been detected in the mucosa and feces of patients with another granulomatous disorder, Crohn's disease. This has led to the successful treatment of resistant Crohn's disease with monoclonal antibodies (Mab) against TNF- $\alpha$ <sup>20</sup>. Similarly, TNF- $\alpha$  plays a central role in the protective host response against tuberculosis, an infectious granulomatous disease<sup>19</sup>. Monoclonal antibody against TNF- $\alpha$  causes a reactivation of tuberculosis in mouse models of latent infection<sup>20</sup> and in humans<sup>22</sup>.

The beneficial and detrimental effects obtained with infliximab in different granulomatous diseases may result from its potential ability to lyse TNF- $\alpha$ -bearing

macrophages or histiocytes in granulomas. Infliximab binds both the monomer and trimer forms of soluble TNF (sTNF) with high avidity and forms stable complexes with the transmembrane form of TNF<sup>23</sup>. Thus, this agent could be expected to improve sarcoidosis and Crohn's disease at the same time that it might facilitate a recrudescence of tuberculosis. Etanercept, a fusion protein of the 75 kDa TNF- $\alpha$  receptor and Fc fragment binds only the trimer form of soluble TNF- $\alpha$ . Etanercept binds to the transmembrane form of TNF- $\alpha$  with less avidity<sup>23</sup>.

In patients with active sarcoidosis<sup>24</sup> the concentrations of soluble TNF receptor, both R1 (55 kDa) and R2 (75 kDa), were elevated. In the subset of patients who responded to corticosteroids, changes in the concentrations of soluble TNF-R2 were more useful for monitoring the inflammatory activity. Thus, the normal response in sarcoidosis may be to increase the levels of soluble TNF receptor in an attempt to prevent the delivery of TNF- $\alpha$  to the cell. Our experience in this case suggests that addition of sufficient amounts of soluble receptor in the form of etanercept may accomplish this goal and ameliorate the disease.

This case report provides further evidence for successful therapy of sarcoidosis with agents directed against TNF- $\alpha$ . Our patient had severe cutaneous and arthritic manifestations of sarcoidosis that improved dramatically with etanercept and prednisone. The etanercept maintained her response after the prednisone was tapered and discontinued.

We doubt that prednisone had a significant role in the improvement of her skin and joint disease given her poor response to intermittent doses of high dose prednisone over the previous 5 years. MTX may have contributed to this excellent response; however, it should be noted that MTX may take up to 6 months to be effective in sarcoidosis<sup>18</sup>. Also, our patient was tapered to very low dose MTX (5 mg/day) after only 3 months of 17.5 mg weekly therapy.

Complex and resistant sarcoidosis may need combination immunosuppressive therapy. Etanercept is a new addition to this armamentarium.

## REFERENCES

- Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336:1224-34.
- Bachwich PR, Lynch JP, Spengler M, Kunkel SL. Tumor necrosis factor production by human sarcoid alveolar macrophages. *Am J Pathol* 1986;125:421-5.
- Muller-Quernheim J, Pfeifer S, Mannel D, Strausz J, Ferlinz R. Lung restricted activation of the alveolar macrophage/monocyte system in pulmonary sarcoidosis. *Am Rev Respir Dis* 1992;145:187-92.
- Ziegenhagen MW, Benner UK, Zissel G, Zabel P, Schlaak M, Muller-Quernheim J. Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med* 1997;156:1586-92.
- Jacyk WK. Cutaneous sarcoidosis in black South Africans. *Int J Dermatol* 1997;38:841-5.
- Gumpel JM, Johns CJ, Shulman LE. The joint disease of sarcoidosis. *Ann Rheum Dis* 1967;26:194-205.
- Barnard J, Newman LS. Sarcoidosis: immunology, rheumatic involvement, and therapeutics. *Curr Opin Rheumatol* 2001; 13:84-91.
- Glennas A, Kvien K, Melby K, et al. Acute sarcoid arthritis: occurrences, seasonal onset, clinical features and outcome. *Br J Rheumatol* 1995;34:45-50.
- Mitchell DN. Sarcoidosis with skeletal involvement. In: Klippel JH, Dieppe PA, editors. *Rheumatology*. London: Mosby International; 1998:26.1-26.8.
- Muthuswamy PP, Lopez-Majano E, Ranginwala V, Trainor WD. Serum angiotensin-converting enzyme activity as an indicator of total body granuloma load and prognosis in sarcoidosis. *Sarcoidosis* 1987;4:142-8.
- Neville E, Carstairs LS, James DG. Sarcoidosis of bone. *QJM* 1977;46:215-27.
- Kaye O, Palazzo E, Grossin M, et al. Low dose methotrexate: An effective corticosteroid-sparing agent in musculoskeletal manifestations of sarcoidosis. *Br J Rheumatol* 1995;34:642-4.
- Kindler V, Sappino A-P, Grau GE, Piguat P-F, Vassali P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell* 1989;115:36-42.
- Baughman RP, Strohofer SA, Buchsbaum J, Lower EE. Release of tumor necrosis factor by alveolar macrophages of patients with sarcoidosis. *J Lab Clin Med* 1990;115:36-42.
- Bost TW, Riches DW, Schumacher B, et al. Alveolar macrophages from patients with beryllium disease and sarcoidosis express increased levels of mRNA for tumor necrosis factor-alpha and interleukin-6 but not interleukin-1 beta. *Am J Respir Cell Mol Biol* 1994;10:506-13.
- Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. *Ann Intern Med* 2001;135:27-31.
- Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001;18:70-4.
- Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. *Am J Med Sci* 1990;299:153-7.
- Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-alpha is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity* 1995;2:561-72.
- Mohan VP, Scanga CA, Yu K, et al. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect Immun* 2001;69:1847-55.
- Stevens C, Walz G, Singaram C, et al. Tumor necrosis factor-alpha, interleukin-1 and interleukin 6 expression in inflammatory bowel disease. *Dig Dis Sci* 1992;37:818-26.
- Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor neutralizing agent. *N Engl J Med* 2001;345:1098-104.
- Scallon B, Cai A, Solowski N, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002;301:418-26.
- Ziegenhagen MW, Fitschen J, Martinet N, Schlaak M, Muller-Quernheim J. Serum level of soluble tumor necrosis factor receptor II (75 kDa) indicates inflammatory activity of sarcoidosis. *J Intern Med* 2000;248:33-41.